A New Environmentally Benign Catalytic Process for the Asymmetric Synthesis of Lactones: Synthesis of the Flavouring δ-Decalactone Molecule

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Received: December 17, 2003; Accepted: February 7, 2004

Abstract: The system Sn-Beta/hydrogen peroxide is applied to the Baeyer–Villiger oxidation of delfone to δ-decalactone, which is an industrial fragrance. The reaction is carried out without solvent and with a substrate/catalyst ratio > 200 (wt/wt). Starting with an enantiomerically enriched delfone it is shown that the rearrangement occurs with retention of configuration at the migrating asymmetric carbon atom, and enantiomerically enriched δ-decalactone is obtained as product. This process offers clear advantages over the actual industrial production that uses peracids as oxidants.

Keywords: Baeyer–Villiger oxidation, δ-decalactone, heterogeneous catalysis, hydrogen peroxide, tin, zeolites

Introduction

Lewis acids have been used for a long time to catalyse selective oxidations.[1] An important breakthrough in the design of heterogeneous oxidation catalysts was the discovery of Ti-silicalite (TS-1).[2] Titanium was incorporated in the framework of silicalite zeolite as isolated tetrahedral Ti(IV) sites. These metal centres are able to form titanium-peroxy species and, thereby, to activate hydrogen peroxide for oxidation reactions such as epoxidation, ammoximation or CH oxidation.[1]

In the course of the exciting oxidation chemistry with TS-1, other metals have been incorporated into molecular sieves, such as vanadium, chromium, zinc, iron, and tin, the latter with an increasing number of applications in recent years. Several patents and reports have appeared on the hydroxylation of phenol with Sn-silicalite,[3] Sn-MCM-41[4] and tin incorporated in other zeolite structures.[5] However, when the results are compared with titanium incorporated into the same molecular sieve the titanium-containing materials always perform better[3b] or much better.[6] Sn-Beta however, was found to be particularly active for Meerwein–Ponndorf–Verley and Oppenauer reactions in which carbonyl groups are reduced and alcohols are oxidised.[7] With respect to epoxidation only the oxidation of the very reactive norbornene has been reported with *tert*-butyl hydroperoxide as oxidant and Sn-MCM-41 as catalyst, while Sn-Beta was found to be absolutely inactive for epoxidation reactions with hydrogen peroxide.[8,9] These results indicate that tin-containing molecular sieves are less effective catalysts for the activation of hydrogen peroxide for oxidation reactions.

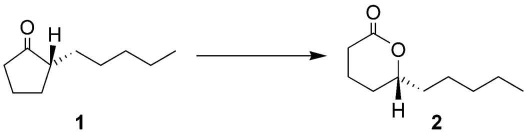
In spite of the lack of activity for an effective hydrogen peroxide activation, we have presented recently a very chemoselective oxidation reaction with hydrogen peroxide catalysed by Sn-Beta,[8,10] namely the Baeyer–Villiger oxidation. This is an important reaction for organic synthesis which finds many applications in the fine chemical industry.[11] It has been demonstrated that the water-resistant heterogeneous Lewis acid Sn-Beta is able to activate the carbonyl group of cyclic ketones and aromatic aldehydes for the nucleophilic attack of hydrogen peroxide to give the corresponding Baeyer–Villiger reaction products.[8b,12] In the case that double bonds were present in the substrate molecules, no epoxidation was observed in contrast to reactions with other classical oxidants such as peracids or MTO/H_2O_2. With tin incorporated into the mesoporous molecular sieve MCM-41 during synthesis or in a post-synthesis treatment, two materials were available without the limitation of molecular size introduced by the pores of the Beta zeolite (6.2–7.2 Å).[13] By *in situ* IR spectroscopy it was established that Sn-Beta has the highest Lewis acid strength of the three materials so that substrates that were able to diffuse within both channel systems without steric impediments were oxidised fastest in the presence of Sn-Beta.

These *in situ* IR measurements provided also valuable information for the proposal of a catalytic cycle. By the coordination of the carbonyl group to the Sn Lewis acid site, the corresponding IR band of the C=O group is

DOI: 10.1002/adsc.200303234

shifted towards lower wavenumbers indicating that the double bond character of the carbonyl bond was decreased, and a higher positive charge appears on the carbon atom. A subsequent nucleophilic attack of the hydrogen peroxide forms a coordinated "Criegee intermediate" or perhydrate. This type of intermediate is in accordance with labelling experiments involving oxygen 18.[8] After a rearrangement step the ester product is obtained. This mechanism has been supported and refined by theoretical calculations revealing further details.[14] A second dative coordination of the Criegee intermediate to the metal centre has been proposed *via* the peroxy oxygen neighbouring the hydrogen atom, with formation of a five-membered ring species. This additional coordination lowers the Gibbs activation barrier for the irreversible Baeyer–Villiger rearrangement (which has been determined in the theoretical work to be the rate-limiting step) since now the leaving group is not the unfavourable water (or hydroxide) but an MOH species. However, these calculations have to be treated cautiously since they have been performed with a very limited zeolite model wherein the whole zeolite network has been substituted by four OH ligands[14] and potential influence or effects of the zeolite structure have been neglected. Furthermore, the results for the epoxidation, where the calculations predict identical behaviour for tin and titanium zeolites, differ significantly from the experimental observations.

In any case, the discovery of Sn-Beta as an active and ecofriendly solid catalyst for Baeyer–Villiger oxidations has opened the possibility for application of the Sn-Beta/H_2O_2 system to the production of some fine chemicals. In this sense, a potential interesting application involves the oxidation of delfone (2-pentylcyclopentanone, **1**) to δ-decalactone (tetrahydro-6-pentyl-2*H*-pyran-2-one, **2**) which has a creamy-coconut and peach-like aroma and is an important flavour constituent of many types of fruit, cheese and other dairy products [Eq. (1)].[15]



(1)

The importance of δ-decalactone is evidenced by the number of bioorganic syntheses[16] or chemical processes[17] which have been patented for its production. The lactone has two different enantiomers, the *R*-isomer being the one found preferentially in nature.[18] As it occurs with other fragrances, in the case of δ-decalactone the two isomers and their racemic mixture have different aromas,[19] and for practical uses the *R*-isomer is the preferred one. Based on this, the industrial production starts with the *R*-isomer enriched ketone, that is transformed into the corresponding lactone by means of a Baeyer–Villiger reaction. Percarboxylic acids are used as oxidants involving a well-established retention of the stereochemistry of an asymmetric migrating centre.[11] However, for the design of a process adapted to the actual environmental demands, peracids should be substituted since they involve several drawbacks such as: a low active oxygen content and therewith important by-product formation, requirement of strong acids,[11] and potential explosions.[20]

A catalytic system like Sn-Beta/hydrogen peroxide could be, in principle, valuable for producing δ-decalactone from the Baeyer–Villiger oxidation of 2-pentylcyclopentanone enriched with the *R*-isomer, if the Sn-Beta catalyst would allow the migration of the asymmetric carbon centre with retention of configuration. In spite of the theoretical and experimental work on the mechanism mentioned above, it is still unknown if this catalyst can be used for oxidation steps in stereoselective synthesis. It is clear that if this point could be clarified and a stereoselective rearrangement could be established and, furthermore, the reaction could be also carried out with aqueous H_2O_2 in absence of any organic co-solvent, a new process for the asymmetric synthesis of lactones and more specifically for the industrial preparation of δ-decalactone could be provided.

Results and Discussion

In order to test the stereochemical behaviour of the rearrangement step, we started with an enantiomerically enriched delfone (87:13) and the Baeyer–Villiger oxidation of this molecule with hydrogen peroxide (35%, 1.5 equivs.) was carried out first in dioxane and with 50 mg of Sn-Beta catalyst for 1 mmol of ketone (ratio ketone/Sn $= 150$ mol mol^{-1}). Time was prolonged to 24 h and reaction temperature lowered to 60 °C with respect to earlier experiments.[8]

Under these experimental conditions, 18% conversion was achieved with a selectivity $> 98\%$. Although the yield was still low, we could already test with the product obtained whether the reaction occurs with retention of configuration at the migrating centre. The two enantiomers were separated with a chiral GC column and an 87:13 ratio was observed, which corresponds to the nominal isomer distribution in the starting ketone (Figure 1). This result proves unequivocally that the Baeyer–Villiger reaction of ketones with a migrating asymmetric carbon atom occurs with retention of the configuration when the oxidation is carried out with hydrogen peroxide and catalysed by Sn-Beta (Figure 2).

Following our second objective, i.e., to avoid the use of any organic co-solvent, the reaction was carried out in a tri-phasic system involving a liquid aqueous phase (hydrogen peroxide), a liquid organic phase (the ketone) and the solid catalyst. Reaction temperature

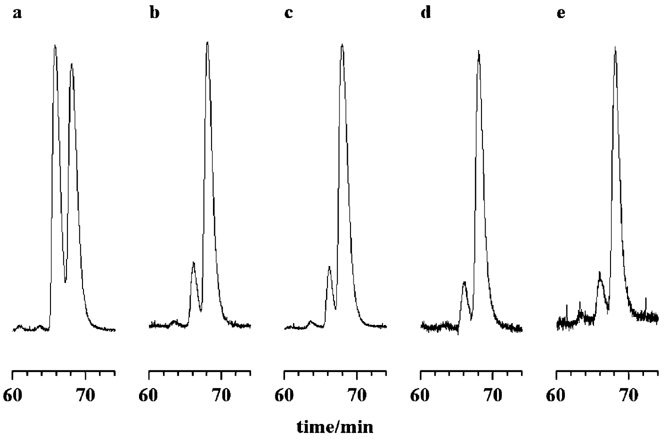


Figure 1. Chromatograms of δ-decalactone obtained from the racemate of delfone by Baeyer–Villiger oxidation with Sn-Beta/H_2O_2 (**a**) and from the enantiomerically enriched delfone by Baeyer–Villiger oxidation with peracetic acid (**b**), with Sn-Beta/H_2O_2 in dioxane (**c**), Sn-Beta/H_2O_2 (**d**), and with Sn-MCM-41/H_2O_2 (**e**).

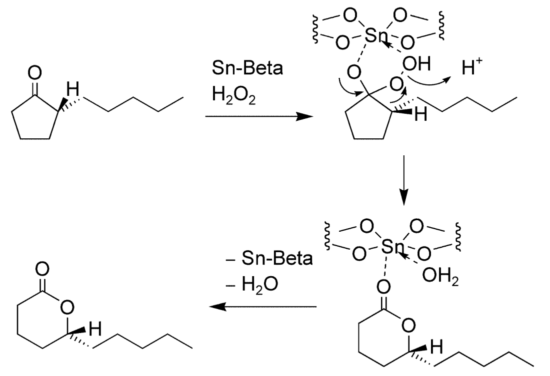
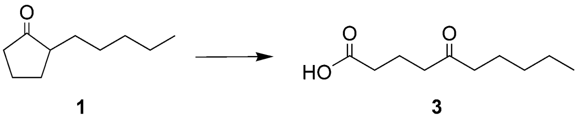


Figure 2. Proposed mechanism for the Sn-Beta catalysed, stereoselective Baeyer–Villiger oxidation with hydrogen peroxide involving an interaction of the hydrogen peroxide with the metal centre improving the leaving group abilities.

was varied from 60 to 110 °C (Table 1) and it is found that increasing the reaction temperature produces a decrease in the reaction selectivity, due to the formation of 5-oxodecanoic acid (**3**), Eq. (2). However, we found that this by-product is not formed catalytically, but by the direct oxidation of the reactant with H_2O_2. Indeed, the blank experiment (Table 1, entry 1) shows that at high reaction temperature 5-oxodecanoic acid as well as other oxidised by-products are formed to a large extent. Therefore, we decreased the reaction temperature to 60 °C, working with a substrate/zeolite ratio of 60 (wt/wt) and a molar ratio H_2O_2/ketone of 1.6. When working without an organic co-solvent under these reactions conditions, the selectivity to the lactone was 86% (with 87 : 13 enantiomeric ratio, Figure 1), while the oxo acid **3** was strongly suppressed (3%). However, the total conversion was 15% after 7 h (Table 1, entry 10). The lactone product obtained with the Sn-MCM-41 catalyst under the same experimental conditions showed the same enantiomeric excess (Figure 1).



(2)

It should be noticed that although the oxo acid is an undesired by-product it may be transformed into lactone **2** by $NaBH_4$ reduction with subsequent H_2SO_4 catalysed cyclisation[21] or by asymmetric reduction providing the *R*-isomer exclusively by use of fermenting baker's yeast.[22] Nevertheless, we attempted to decrease the yield of **3** by decreasing by 50% the concentration of oxidant (H_2O_2). Thus, by doing this and working at 90 °C the selectivity towards lactone **2** could be improved from 61% to 80% and the yield increased from 26% to 30% (Table 2, entries 2 and 3). A further reduction of the oxidant to only 0.3 equivalents improved further the

Table 1. Conversions and selectivities for the Baeyer–Villiger oxidation of delfone with hydrogen peroxide (35%)/Sn-Beta in a tri-phasic system after 7 h at different temperatures. Reaction conditions: 3.0 g (19 mmol) of delfone, 3.0 g (30 mmol) of 35% aqueous hydrogen peroxide, and 50 mg of Sn-Beta catalyst were mixed and heated to the desired reaction temperature.

Entry	Catalyst [mg]	Temp. [^{0}C]	Conv. [%]	Selectivity [%]			Yield [%]	
				2	**3**	other	**2**	**3**
1	–	110	36	27	36	37	10	13
2	50	110	57	52	30	18	30	17
3	–	90	21	32	43	25	7	9
4	50	90	43	61	22	17	26	9
5	–	80	10	24	42	34	2	4
6	50	80	37	69	14	17	25	5
7	–	70	3	24	28	48	1	1
8	50	70	21	73	7	20	15	2
9	–	60	1	41	11	48	0.4	0.1
10	50	60	15	86	3	11	13	0.5

Table 2. Conversions and selectivities for the Baeyer–Villiger oxidation of delfone with different amounts of hydrogen peroxide (35%) and Sn-Beta in a tri-phasic system after 7 h at 90 °C. Reaction conditions: 3.0 g (19 mmol) of delfone, the corresponding amount of 35% aqueous hydrogen peroxide, and 50 mg of Sn-Beta catalyst were mixed and heated to 90 °C.

Entry	**1**/cat[a] [wt/wt]	H_2O_2 [equiv.]	Conv. [%]	Selectivity [%]			Yield [%]	
				2	**3**	other	**2**	**3**
1	60	0.3	17	92	0	8	16	0
2	60	0.8	38	80	11	9	30	4
3	60	1.6	43	61	22	17	26	9

[a] Substrate/catalyst ratio.

Table 3. Conversions and selectivities for the Baeyer–Villiger oxidation of delfone with hydrogen peroxide (1.6 equivs., 35%) and Sn-Beta in a tri-phasic system after 7 h at 80 °C in the presence of different amounts of Na_2HPO_4. Reaction conditions: 3.0 g (19 mmol) of delfone, 3.0 g (30 mmol) of 35% aqueous hydrogen peroxide, 50 mg of Sn-Beta catalyst, and the corresponding amount of Na_2HPO_4 were mixed and heated to 80 °C.

Entry	Na_2HPO_4 [mg]	Conv. [%]	Selectivity [%]			Yield [%]	
			2	**3**	other	**2**	**3**
1	0	37	69	14	17	25	5
2	152	23	75	14	11	17	3
3	303	10	80	5	15	5	0.5
4	600	10	77	3	20	3	0.3

selectivity towards lactone **2**, however, the conversion and therewith the yield dropped significantly (Table 2, entry 1). A slow addition during seven hours of the hydrogen peroxide did not improve the catalytic performance.

In another attempt to reduce the formation of the oxo acid **3**, the acidity of the H_2O_2 was reduced by adding Na_2HPO_4. The results from Table 3 show an increase of the selectivity to lactone, but the conversion was negatively affected.

At this point, and in order to increase conversion and selectivity, always working with a tri-phasic system, we increased the catalyst to substrate ratio in order to improve the relative rates of the catalysed (lactone) versus the uncatalysed (oxy acid) reaction, while working at different reaction times. From the results given in Table 4, it can be seen that it is possible to achieve near 100% conversion of the ketone, with a selectivity of 84% to the lactone at 60 °C and with a substrate to zeolite ratio of 10, which results in a molar ratio of substrate to active Sn site of 488. In a further up-scale at prolonged reaction time, 107 g of (±)-delfone were employed along with 2.1 equiv. of 50% aqueous hydrogen peroxide and 500 mg of Sn-Beta at 60 °C. With the resulting substrate/catalyst ratio of 200 (wt/wt) full conversion was achieved after 54 h and 86% of the desired product was observed.

Conclusion

In summary, we can say that during the Baeyer–Villiger oxidation of ketones with only one enantiomer or in an enantiomerically enriched mixture, using an Sn-Beta catalyst and H_2O_2, the migration of the asymmetric carbon centre occurs with retention of configuration. We have also shown that the Baeyer–Villiger oxidation of 2-pentylcyclopentatone (**1**) to δ-decalactone (**2**) can be performed with H_2O_2 and Sn-Beta zeolite catalyst, without requiring any co-solvent. A process such as the one reported here appears interesting also from an industrial point of view.

Experimental Section

Hydrogen peroxide (50%) was purchased from Aldrich and hydrogen peroxide (35%) from Fluka. Delfone and enantiomerically enriched delfone were provided by Acedesa. As the enantiomeric excess of the enriched ketone was not known exactly, the Baeyer–Villiger oxidation was carried out with peracetic acid and the lactone product analysed as in the other cases (Figure 1). The obtained ratio was taken also for the ketone substrate since it is well known in the literature that the Baeyer–Villiger oxidation with peracids occurs with retention of configuration.[11] Sn-Beta was synthesised according to the literature procedure.[8] The Sn content (2.0 wt % of SnO_2) was determined by atomic absorption. The Sn-Beta zeolite was calcined at 853 K for 3 h. A high crystallinity of the zeolite was observed by XRD, and no peaks of SnO_2 were found in the

Table 4. Conversions and selectivities for the Baeyer–Villiger oxidation of delfone with hydrogen peroxide (1.6 equivs., 35%) and Sn-Beta in a tri-phasic system after 7 h at 60 °C with different catalyst amounts. Reaction conditions: 3.0 g (19 mmol) of delfone, 3.0 g (30 mmol) of 35% aqueous hydrogen peroxide, and 0 mg, 50 mg, 100 mg, and 200 mg of Sn-Beta catalyst (for entries 1 to 4, respectively) were mixed and heated to 60 °C. For entries 5 to 7, 1.0 g (6.5 mmol) of delfone, 1.0 g (15 mmol) of 50% aqueous hydrogen peroxide, and 100 mg of Sn-Beta catalyst were mixed and heated to 60 °C.

Entry	**1**/cat[a] [wt/wt]	Time [h]	Conv. [%]	Selectivity [%]			Yield [%]	
				2	**3**	other	**2**	**3**
1	[b]	7	1	41	11	48	0.4	0.1
2	60	7	15	86	3	11	13	0.5
3	30	7	26	76	10	14	20	2
4	15	7	29	78	8	16	22	2
5	10[c]	7	58	84	4	12	49	2
6	10[c, d]	7	32	96	0	4	31	0
7	10[c]	24	95	84	8	8	80	7

[a] Substrate/catalyst ratio.
[b] Without catalyst.
[c] 2.3 equivs. hydrogen peroxide were used as 50% aqueous solution.
[d] With dioxane as solvent.

diffractogram. Nitrogen adsorption experiments on the calcined Beta samples gave an isotherm very similar to that of pure silica Beta with values of micropore volume of 0.20–0.21 $cm^3 g^{-1}$ and BET surface areas of 450–475 $m^2 g^{-1}$. GC analyses were carried out on an HP 5890 gas chromatograph equipped with a 25 m HP-5 column. GC-MS analyses for the identification of products were carried out on an Agilent Technologies 6890N apparatus coupled with an Agilent Mass Selective Detector 5973 Network. ^{1}H NMR spectra were recorded with a Bruker spectrometer at a frequency of 300 MHz and ^{13}C NMR spectra at a frequency of 75 MHz. The two enantiomers of δ-decalactone were separated on a Fisons Instruments GC 8035 equipped with an Chiraldex G-TA (gamma-cyclodextrin, trifluoroacetylated) column from Astec (30 m, 0.25 mm, 0.25 μm film) at 125 C isothermally.

General Procedure for the Baeyer–Villiger Oxidation

Delfone, aqueous hydrogen peroxide (35% or 50%), optionally 3.0 g of dioxane and Sn-Beta catalyst (normally 50 mg) were stirred magnetically and heated to the desired reaction temperature. The reaction was followed by gas chromatography, and the products were identified by comparison with reference samples, by GC-MS, or after purification by ^{1}H NMR spectroscopy.

Lactone 2: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.89$ (t, $J = 6.7$ Hz, 3H, 10-H), 1.3–1.9 (m, 12H, 3-H, 4-H, 6-H, 7-H, 8-H, 9-H), 2.4–2.7 (m, 2H, 2-H), 4.3 (m, 1H, 5-H).

For the identification of the oxo acid **3**, the organic phase of the catalytic run at 70 °C was distilled in an oil-pump vacuum. The residue, colourless crystalline material, was submitted to NMR analysis: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 0.89$ (t, $J = 7.1$ Hz, 3H, 10-H), 1.29 (m, 4H, 9-H, 8-H), 1.65 (m, 2H, 7-H), 1.90 (quin., $J = 7.1$ Hz, 2H, 3-H), 2.39 (t, $J = 7.2$ Hz, 2H, 4-H or 6-H), 2.40 (t, $J = 7.8$ Hz, 2H, 4-H or 6-H), 2.50 (t, $J = 7.2$ Hz, 2H, 2-H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 13.9$ (q, C-10), 18.5 (t, C-3), 22.4 (t, C-9), 23.5 (t, C-7), 31.4 (t, C-8), 33.0 (t, C-2), 41.3 (t, C-4), 42.8 (t, C-6), 178.9 (s, C-1), 210.5 (s, C-5).

Acknowledgements

The authors thank Acedesa, CICYT (MAT2003–07945-C02–01), and the Generalitat Valenciana for financing this work. M. R. is grateful to the Spanish Ministry of Science and Technology for a "Ramón y Cajal" Fellowship.

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